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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/752,293	12/28/2000	Alex Chenchik	CLON017US1	6681

24353 7590 09/23/2003

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EXAMINER	
MYERS, CARLA J	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/752,293	CHENCHIK ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-13,15-19 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-13,15-19 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on May 6, 2003 has been entered.

Claims 1-5, 7-13, 15-19 and 21 are pending. All previous grounds of rejection are withdrawn. However, this office action contains the following new grounds of rejection and is made non-final.

2. The terminal disclaimer filed on January 21, 2003 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent granted on U. S. Application No. 09/752,292 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 7-12, 15, 16, 19 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5 and 7-12 are indefinite over the recitation of "detecting any resultant hybridization complexes" because the claims include only a contacting step and not a step in which complexes are formed and the claims do not clearly set forth what constitutes the hybridization complex that is to be detected. In claim 1, step (b) should be amended to clarify that the contacting step results in the formation of a complex between the tagged target nucleic acids and tag complements immobilized on the planar surface.

Claim 2 is indefinite over the recitation of "wherein said tagged gene specific primers are not used in an amplification step" because it is not clear as to how this recitation further limits and relates back to claim 1. It is not clear as to whether this recitation is intended to limit step a) such that the population or tagged target nucleic acids is not generated via an amplification step or if this recitation refers to not using the primers for amplification outside of the three steps recited in the method of claim 1.

Claims 3 and 7-9 are indefinite over the recitation of "hybridization efficiency between any two tag-tag complement pairs" because the claim does not specifically refer to the formation of "tag-tag complement pairs." Rather, the claim refers only to a step of contacting a tagged nucleic acid with a tag complement immobilized on a planar surface. The claim does not include a step of forming a complex between these molecules and specifically does not refer to the formation of a "tag-tag complement pair."

Claim 4 is indefinite over the recitation of "any tag employed in the assay has a level of cross-hybridization that does not exceed about 10%" because the claim does

not define the molecule to which the tag does nor does not cross-hybridize. Does the tag not cross-hybridize with other tags, or with the target nucleic acid or with a tag complement that is immobilized or attached to the target nucleic acid? Since the assay as defined in the specification includes a step in which the tag forms a complex with a tag complement immobilized on the support, it is confusing to generically refer to the tag as having a level of cross-hybridization that does not exceed 10%.

Claim 12 is indefinite over the recitation of "wherein said assay comprises" because it is not clear as to whether this step occurs in addition to step (a) of claim 1 or if this recitation serves to further characterize step (i.e., wherein said generating step comprises...).

Claim 15 is indefinite over the recitation of "hybridization efficiency between any two tag-tag complement pairs taken from said array" because the claim does not specifically refer to "tag-tag complement pairs." It is also unclear as to what is meant by the set of gene specific primers not having any difference in hybridization efficiency that exceeds 10 fold. Does this refer to the relationship between the different gene specific primers or to the relationship between a gene specific primer and a tag complement?

Claim 16 is confusing over the recitation of "any tag found in said set of tagged gene specific primers has a level of cross-hybridization with respect to said array" because it is not clear as to what is meant by a tag not cross-hybridizing with the array. It is not clear as to whether this recitation refers to the tagged gene specific primers not

cross-hybridizing with the solid support itself or not cross-hybridizing with tag complements bound to the support.

Claims 19 and 21 are indefinite over the recitation of "wherein said tag complements are members of a collection of tag-tag complement pairs" because it is not clear as to how this recitation relates to the array. It is not clear as to whether the array comprises tag-tag complement pairs or only the tag complements. The claims do not clarify the relationship between the tag-tag complement pairs and the tagged target nucleic acid.

Claim 21 is indefinite over the recitation of "said array has a density that does not exceed about 400 spots/cm^2" because it is not clear as to what the relationship is between the spots on the array and the tag complements.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 7-12, 19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balch et al (US. Patent No. 6,331,441).

Balch teaches methods for detecting a target nucleic acid wherein said methods comprise immobilizing a nucleic acid capture probe (i.e. a nucleic acid "tag") onto a solid support to form an array of distinct nucleic acid capture probes, contacting a nucleic acid sample with a primer consisting of a first region that is complementary to the capture probe and a second region that is specific for a target nucleic acid (i.e., a "tagged gene specific primer"), extending said primer via a method such as PCR or LCR to generate a population of nucleic acids having a sequence complementary to the capture probe, hybridizing the extended nucleic acids with the array of capture probes and detecting hybridization between the capture probes and the extended target nucleic acids (see columns 21, and 33-35). Balch also teaches methods in which the capture probes are contacted with a collection of target probe/primers that are hybridized with complementary target nucleic acids and detecting the complexes formed between the capture probe and the target probe/primer-target nucleic acid as indicative of the presence of the target nucleic acid. Balch states that when a primer with a sequence complementary to the capture probe sequence is used in the assay, an amplification product with tails complementary to capture probe sites in the array is created and after amplification, the resulting amplicon can be directly hybridized to the capture probe array and analyzed (column 21). Balch states that "(f)or capture probe sets, it is

desirable to obtain a set structure such that each member of the probe set is maximally dissimilar from all others" (see column 18). The capture probe set may comprise 24 or 36 or 48 etc distinct probes. Furthermore, the capture probes are designed so that they minimize cross-hybridization between the capture probe and the specific target nucleic acid. Balch also teaches how to select capture probes so that they will be maximally dissimilar but so that they also have very similar G/C contents and probe lengths. This results in capture probe sets that hybridizes with similar efficiency to the specific 5' complementary capture tail attached to the target nucleic acid and minimizes cross-hybridization between the target nucleic acid itself and the capture probes (see, for example, columns 17-19). With respect to the target probe/primer (i.e., the primer having a region complementary to the capture probe and a region specific for the target nucleic acid), Balch teaches that the target specific sequence should have less than 80% identity with the capture probe sequence and also teaches that each target probe/primer binds to only one element of the capture probe set (columns 20-21). Balch does not exemplify as a single embodiment a hybridization assay comprising generating a population of tagged nucleic acids using a collection of at least 20 distinct target probe/primers (i.e., 20 distinct "tagged gene specific primers"). However, Balch does suggest using the disclosed assay to detect multiple target nucleic acids and teaches that the capture probe set may comprise 24 or more distinct sequences and that the target probe/primer is selected to bind to only one of each of the capture probe sequences. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have practiced the method of Balch using at least 20

distinct capture probes and at least 20 distinct target probes/primers in order to have generated an effective method for simultaneously analyzing for the presence of 20 or more distinct target nucleic acids.

With respect to claim 2, Balch teaches that in one embodiment, the target probe/primer is used to amplify the target nucleic acid by PCR or LCR prior to the step of contacting the array of capture probes with the target probe/primer. Balch also teaches alternative methods for detecting the target nucleic acid wherein the target probe/primer is extended in a sequencing reaction (e.g. columns 33-35). Additionally, Balch teaches methods in which the target probe/primer is hybridized with a target nucleic acid and this complex is contacted with the capture probe array and the formation of a hybridization complex between the capture probe and target probe/primer-target nucleic acid is detected as indicative of the presence of the target nucleic acid. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Balch so as to have omitted the step of amplifying the DNA prior to detecting the nucleic acids in reactions in which sufficient quantities of the target nucleic acid were present so as to have provided a simpler and faster means for detecting the target nucleic acid.

Furthermore, with respect to claim 5, Balch teaches labeling the target nucleic acid by using a labeled primer to extend the nucleic acid (see, for example, columns 25-26 and 33-36). With respect to claim 11, Balch teaches that the target nucleic acid may be RNA (see column 24). With respect to claim 12, Balch teaches that the target nucleic acid may be derived from 2 or more samples, such as samples obtained from different

patients (see, for example, columns 34 and 37-38). With respect to claim 21, Balch teaches that the capture probes may be spotted on the array at a density of about 100 probes/cm^2.

With respect to claims 3, 4 , 7-10, 19 and 20, Balch does not specifically teach that the difference in efficiency between the capture probes does not exceed 10 or 5 or 3 fold and does not teach that the level of cross-hybridization between the capture probes and target nucleic acid is less than 10% or 2% or 1%. However, Balch does stress the importance of selecting capture probes that do not cross-hybridize with the target nucleic acid so as to ensure the specificity and accuracy of the detection assay. Balch also teaches that the capture probes are selected so that they have similar G/C contents and lengths. Techniques for selecting and optimizing probes so as to enhance hybridization efficiencies and reduce cross-hybridization were well known in the art at the time the invention was made. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have selected capture probes with differences in the efficiency of hybridization of less than 10 or 5 or 3 fold and to select capture probes which had levels of cross-hybridization of less than 10% or 2% or 1% in order to have provided the advantages of generated a highly specific and accurate means for detecting target nucleic acids.

5. Claims 13 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balch et al (US. Patent No. 6,331,441) in view of Chenchik (US Patent No. 5,994,076).

The teachings of Balch are presented above. Balch teaches methods which require the use of an array of at least 20 distinct capture probes immobilized on a solid surface; a set of at least 20 target probe/primers specific for a target nucleic acid and having a region complementary to the capture probe; and a means for identifying the physical location of each capture probe on the array. Balch does not teach packaging the reagents required to perform the detection method in a kit.

However, reagent kits for performing diagnostic methods were well known in the art at the time the invention was made. For example, Chenchik teaches methods for detecting a target nucleic acid wherein a gene specific primer, including a primer having an anchor sequence, is used to extend a target nucleic acid and an array is used to detect the extended nucleic acid. Chenchik teaches packaging the reagents required to perform the array detection method into a kit (see column 13).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have packaged the reagents required to practice the method of Balch in a kit and particularly to have included in the kit an array of at least 20 distinct capture probes immobilized on a solid surface; a set of at least 20 target probe/primers specific for a target nucleic acid and having a region complementary to the capture probe; and a means for identifying the physical location of each capture probe on the array, in order to have provided the advantages of cost-effectiveness and convenience for practioners in the art wishing to practice Balch's method for detecting target nucleic acids. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have included information regarding the

location and identity of the capture probes on the array because it would have been clear that this information would have been necessary for practioners in the art to use the array and to analyze the results of the array.

6. Claims 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balch et al (US. Patent No. 6,331,441) in view of Chenchik (US Patent NO. 5,994,076) and further in view of Kamb (6,060,240).

The teachings of Balch and Chenchik are presented above. The combined references do not teach including in a kit a website address for remotely accessing information regarding the physical location of the capture probes.

However, Kamb teaches methods for detecting a target nucleic acid using an array. Kamb teaches that nucleic acid sequence databases and sequence analysis packages are available via the Internet and can be used to solve the problems of data storage and sequence analysis.

In view of the conventionality in the art of using public databases to store and disseminate information, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have included a website address in the kit for performing the method of Balch in order to have provided a readily accessible means for providing information regarding the identity and location of capture probes on the array and for analyzing the results of assays using the array of Balch.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers
September 17, 2003

CARLA J. MYERS
PRIMARY EXAMINER